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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p><b>(21) International Application Number:</b> PCT/US97/07985</p> <p><b>(22) International Filing Date:</b> 13 May 1997 (13.05.97)</p> <p><b>(30) Priority Data:</b></p> <table border="0"> <tr> <td>60/017,891</td> <td>17 May 1996 (17.05.96)</td> <td>US</td> </tr> <tr> <td>9612065.4</td> <td>10 June 1996 (10.06.96)</td> <td>GB</td> </tr> </table> <p><b>(71) Applicants (for all designated States except US):</b> MERCK &amp; CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).</p> <p><b>(72) Inventors; and</b></p> <p><b>(75) Inventors/Applicants (for US only):</b> HANCOCK, Bruno [GB/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). WINTERS, Conrad [GB/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GERTZ, Barry [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GOTTESDIENER, Keith [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p><b>(74) Common Representative:</b> MERCK &amp; CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p>		60/017,891	17 May 1996 (17.05.96)	US	9612065.4	10 June 1996 (10.06.96)	GB	<p><b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p>
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9612065.4	10 June 1996 (10.06.96)	GB						
<p><b>(54) Title:</b> COMPOSITIONS FOR A ONCE A DAY TREATMENT OF CYCLOOXYGENASE-2 MEDIATED DISEASES</p> <p><b>(57) Abstract</b></p> <p>This invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone. The invention is also directed to a method of treating cyclooxygenase-2 mediated diseases comprising the once a day oral administration of 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone. The invention is also directed to the use of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a medicament containing 2.5 to 250 mgs of said compound for once a day administration for the treatment of cyclooxygenase-2 mediated diseases.</p>								

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## TITLE OF THE INVENTION

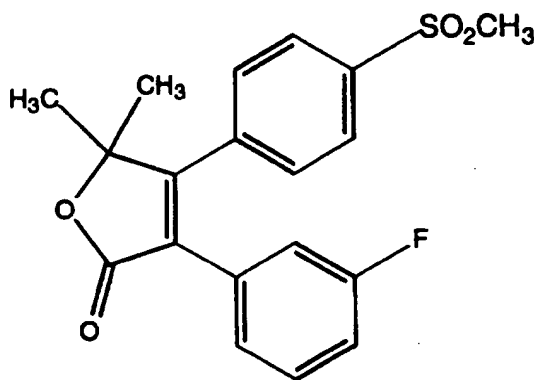
### COMPOSITIONS FOR A ONCE A DAY TREATMENT OF CYCLOOXYGENASE-2 MEDIATED DISEASES

#### 5 BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions for the treatment of cyclooxygenase-2 mediated diseases, methods of treatment thereof and the use of a compound in the manufacture of a medicament.

10 In particular, this invention relates to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day administration, said composition comprising

15 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-(5H)-furanone.



Non-steroidal anti-inflammatory agents are normally administered 2 to 4 times daily. The relatively short half-life of most non-steroidal anti-inflammatory agents means that once a day administration is impractical and even twice a day administration is unusual. The relatively large doses needed to achieve once a day treatment of conventional non-steroidal anti-inflammatory agents would also lead to side effects so that there is a general understanding that once a day administration is unlikely to be achievable.

25 Surprisingly a compound has been identified which can be employed on a once a day basis and which will not produce an

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unacceptable level of side effects on such a regimen, and in particular will not cause an unacceptable level of gastric side effects.

US 5,474,995, issued December 12, 1995, WO 95/00501, published January 5, 1995 and WO 95/18799, published July 13, 1995, disclose 3,4-di-substituted furanones and derivatives thereof as potent, selective inhibitors of cyclooxygenase-2. We have found that 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, possesses a surprising combination of attributes that make it possible to formulate and use the composition in a surprising manner. Not only is the compound potent, safe and effective at modest oral dosages of 2.5 to 250 mg of agent per day, but in addition this active agent possesses a half-life in humans of sufficient length that a single oral dose of 2.5 to 250 mg of agent per day will provide effective safe anti-inflammatory treatment over a 24 hour period. Such active agents are particularly useful in the treatment of chronic indications, including arthritis, pain, Alzheimer's disease and the like.

#### SUMMARY OF THE INVENTION

This invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

The invention is also directed to a method of treating cyclooxygenase-2 mediated diseases comprising the once a day oral administration of 2.5 to 250 mgs of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

The invention is also directed to the use of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a medicament containing 2.5 to 250 mgs of said compound for once a day administration for the treatment of cyclooxygenase-2 mediated diseases.

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**DETAILED DESCRIPTION OF THE INVENTION**

In one embodiment, this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising 2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, and a pharmaceutical carrier therefor.

5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, its utility and methods of making them are disclosed in US 5,474,995, issued December 12, 1995, WO 95/00501, published January 5, 1995 and WO 95/18799, published July 13, 1995, which are hereby incorporated by reference.

As discussed in US 5,474,995 compounds including 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone are useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. It is also useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer's Disease (ie Alzheimer's dementia).

The compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its potent inhibitory activity against cyclooxygenase-2 (COX-2) and/or its selectivity for inhibiting COX-2 over cyclooxygenase-1 (COX-1) the specified compound is also useful

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as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such NSAIDS may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of  
5 gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to surgery or taking anticoagulants; and those susceptible to NSAID  
10 induced asthma.

For the treatment of any of these cyclooxygenase mediated diseases the compound may be administered orally.

As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one  
15 or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or  
20 elixirs. The compositions are intended for oral use and may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to  
25 provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium  
30 phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc.



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Other suitable formulations are set forth in U.S. Patent No. 5,474,995. However, in view of the unique set of properties possessed by 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone, including long half-life, low solubility, high potency and de minimis gastrointestinal (GI) side effects we have found the following oral formulations to be of particular value:

Rapidisc® – In view of the above mentioned characteristics, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone is particularly well suited for a rapid dissolving sublingual formulation. For example, due to the lack of GI side-effects, the agent need not be taken with a large amount of water. Suitable Rapidisc® formulations and methods of making same are disclosed in US 4,305,502, US 4,371,516, US 4,470,202, US 4,758,598, US 4,754,597, US 5,046,618 and US 5,188,882, all of which are hereby incorporated by reference.

As mentioned in the Background section, we have found 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone to possess a surprising combination of attributes. Not only are these active agents potent safe and effective at modest oral dosages of 2.5 to 250 mg of agent per day, but in addition these active agents possess a half-life in humans of sufficient length that a single oral dose of 2.5 to 250 mg of active agent per day will provide effective safe anti-inflammatory treatment over a 24 hour period. Such agents are particularly useful in the treatment of chronic indications, such as rheumatoid and osteo arthritis as well as Alzheimer's Disease.

Oral dosage levels for agents 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone are of the order of from about 2.5 to 250 mg per patient per day.

The amount of active agent that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from 2.5 to 250 mg of agent compounded with an appropriate and convenient amount of carrier material which may vary from about

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5 to about 95 percent of the total composition. Dosage unit forms may typically contain 2.5, 5, 10, 12.5, 20, 25, 37.5, 50, 75, 100, 125, 150, 175 or 250 mg of active agent.

It will be understood, however, that the specific dose level  
5 for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination and the type and severity of the particular disease undergoing therapy. For many patients, a dosage range of 2.5 to 125 or 10 to 75 mg per day is  
10 preferred.

For long term therapy, such as in the treatment of chronic diseases including rheumatoid arthritis, osteoarthritis or Alzheimer's disease, a dosage of 10 to 75 or 5 to 125 mg per day is preferred. More particularly, for the treatment of osteoarthritis, a dosage of 10, 25 or 50  
15 mg per day is preferred, whereas for the treatment of rheumatoid arthritis, 25, 50 or 75 mg per day is preferred. For the treatment of non-chronic indications such as headache or post-operative swelling and pain, 5, 10, 25 or 50 mg per day is preferred.

Accordingly, in one aspect this invention is directed to a  
20 pharmaceutical composition for the treatment of COX-2 mediated diseases, said composition being suitable for once a day oral administration, said composition comprising a 2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, and a pharmaceutical carrier therefor.

25 Within this aspect there is a first genus of compositions comprising 5, 10 or 25 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

Within this aspect there is a second genus of compositions comprising 10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.  
30

Within this genus there is a class of compositions comprising 10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

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Within this genus there is a second class of compositions comprising 10, 25, or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

5 Within this genus there is a third class of compositions comprising 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

In another aspect the invention is directed to a unit dose oral form which comprises from 5 to 22.5 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone, for  
10 example, 12.5 or 20 mg.

### EXAMPLE 1

#### Wet granulated tablet composition

15	Amount per tablet	Ingredient
	25 mg	COX-2 Inhibitor
	79.7 mg	Microcrystalline cellulose
	79.7 mg	Lactose monohydrate
20	6 mg	Hydroxypropyl cellulose*
	8 mg	Croscarmellose sodium
	1 mg	Magnesium stearate

25 Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

\* Klucel®LF® from Aqualon

30

### EXAMPLE 1a

#### Wet granulated tablet composition

35	Amount per tablet	Ingredient
	12.5 mg	COX-2 Inhibitor
	86 mg	Microcrystalline cellulose
	86 mg	Lactose monohydrate

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6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

5

**EXAMPLE 1b****Wet granulated tablet composition**

10	Amount per tablet	Ingredient
	10 mg	COX-2 Inhibitor
	87.2 mg	Microcrystalline cellulose
	87.2 mg	Lactose monohydrate
15	6 mg	Hydroxypropyl cellulose
	8 mg	Croscarmellose sodium
	1 mg	Magnesium stearate

20

**EXAMPLE 1c****Wet granulated tablet composition**

	Amount per tablet	Ingredient
25	5 mg	COX-2 Inhibitor
	89.7 mg	Microcrystalline cellulose
	89.7 mg	Lactose monohydrate
	6 mg	Hydroxypropyl cellulose
30	8 mg	Croscarmellose sodium
	1 mg	Magnesium stearate

**EXAMPLE 2****Directly compressed tablet composition**

	Amount per tablet	Ingredient
35	25 mg	COX-2 Inhibitor
40	106.9 mg	Microcrystalline cellulose

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106.9 mg	Lactose anhydrate
7.5 mg	Croscarmellose sodium
3.7 mg	Magnesium stearate

- 5 Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

10 EXAMPLE 2a

Directly compressed tablet composition

	Amount per tablet	Ingredient
15	12.5 mg	COX-2 Inhibitor
	113.2 mg	Microcrystalline cellulose
	113.2 mg	Lactose anhydrate
	7.5 mg	Croscarmellose sodium
20	3.7 mg	Magnesium stearate

EXAMPLE 2b

Directly compressed tablet composition

	Amount per tablet	Ingredient
25	10 mg	COX-2 Inhibitor
	42.5 mg	Microcrystalline cellulose
30	42.5 mg	Lactose anhydrate
	4 mg	Croscarmellose sodium
	1 mg	Magnesium stearate

EXAMPLE 2c

35 Directly compressed tablet composition

	Amount per tablet	Ingredient
40	5 mg	COX-2 Inhibitor

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45 mg	Microcrystalline cellulose
45 mg	Lactose anhydrate
4 mg	Croscarmellose sodium
1 mg	Magnesium stearate

5

**EXAMPLE 3****Hard gelatin capsule composition**

10	Amount per capsule	Ingredient
	25 mg	COX-2 Inhibitor
	37 mg	Microcrystalline cellulose
	37 mg	Lactose anhydrate
15	1 capsule	Hard gelatin capsule
	1 mg	Magnesium stearate

Capsule dose strengths of between 1 and 50 mg can be accommodated by varying total fill weight, and the ratio of the first three ingredients.

20 Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

**EXAMPLE 4**

25

**Oral solution**

	Amount per 5 mL dose	Ingredient
30	50 mg	COX-2 Inhibitor
	To 5 mL with Polyethylene oxide 400	

Solution dose strengths of between 1 and 50 mg/5mL can be accommodated by varying the ratio of the two ingredients.

35

**EXAMPLE 5****Oral suspension**

40	Amount per 5 mL dose	Ingredient
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	101 mg	COX-2 Inhibitor
	150 mg	Polyvinylpyrrolidone
	2.5 mg	Poly oxyethylene sorbitan monolaurate
5	10 mg	Benzoic acid
	To 5 mL with sorbitol solution (70%)	

Suspension dose strengths of between 1 and 50 mg/5mL can be accommodated by varying the ratio of the first and last ingredients.

10

EXAMPLE 6Intravenous infusion

	<b>Amount per 200mL dose</b>	<b>Ingredient</b>
15	1 mg	COX-2 inhibitor
	0.2 mg	Polyethylene oxide 400
	1.8 mg	Sodium chloride
	to 200mL	Purified water

20

STARTING MATERIALS

5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone

25

Step 1: Methyl 2-trimethylsilyloxyisobutyrate

To a solution of 1.2 mL (10.4 mmol) of methyl 2-hydroxyisobutyrate in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> were added 1.2 g (17.6 mmol) of imidazole and 2.1 mL (16.6 mmol) of TMSCl. The mixture was stirred at r.t. for 1.5 h and quenched with 20 mL of H<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub>, concentrated and passed through a short plug of silica gel eluted with 9:1 hexane/EtOAc. Evaporation of solvent afforded 1.27 g of the title compound as a colorless oil.

35

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.08 (9H, s), 1.38 (6H, s), 3.67 (3H, s).

Step 2: 2-Trimethylsilyloxy-4'-(methylthio)isobutyrophenone

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A solution of 204 mg (1.0 mmol) of 4-bromothioanisole in 2.5 mL of THF was cooled to -78°C and treated with 0.42 mL of 2.5 M n-BuLi solution in hexane. After stirring at -78°C for 1 h, a solution of 380 mg (2.0 mmol) of methyl 2-trimethylsilyloxyisobutyrate (Step 1) in 2 mL of THF was added. The mixture was stirred at -78°C for 2 h and then quenched with NH<sub>4</sub>OAc buffer. The product was extracted with EtOAc, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography, eluting with 19:1 hexane/EtOAc to give 95 mg of the title product.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 0.05 (9H, s), 1.52 (6H, s), 2.53 (3H, s), 7.33 (2H, d), 8.12 (2H, d).

**Step 3: 2-Hydroxy-4'-(methylthio)isobutyrophenone**

To a solution of 40 mg (0.14 mmol) of 2-trimethylsilyloxy-4'-(methylthio)isobutyrophenone (Step 2) in 2 mL THF was added 0.2 mL of 1 M n-Bu<sub>4</sub>NF in THF. The resulting mixture was stirred for 30 min and then quenched with 10 mL of NH<sub>4</sub>OAc buffer. The product was extracted with EtOAc, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography, eluting with 4:1 hexane/EtOAc to give 25 mg of the title product.

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 1.50 (6H, s), 2.54 (3H, s), 4.68 (1H, s), 7.30 (2H, d), 8.15 (2H, d).

**Step 4 2-hydroxy-4'-(methylsulfonyl)isobutyrophenone**

To a solution of 2-hydroxy-4'-(methylthio)isobutyrophenone (Step 3) (45 g) in t-BuOH (500 mL) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added a solution of OXONE™ (194 g) in H<sub>2</sub>O (1.4 L). The reaction mixture was stirred for 18 h at r.t. and then extracted with EtOAc (3 x 500 mL). The organic extracts were combined and dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. The residue was swished in Et<sub>2</sub>O/hexane to give the title compound as a yellow solid (47.4 g).

**Step 5 3-Fluorophenylacetic acid, 1,1-dimethyl-2-(4-(methylsulfonyl)phenyl)-2-oxo-ethyl ester**



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A mixture of 2-hydroxy-4'-(methylsulfonyl)isobutyrophenone (Step 4) (100 g), 3-fluorophenylacetic acid (83 g), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate (225 g) and DMAP (25 g) in CH<sub>2</sub>Cl<sub>2</sub> (2 L) was mechanically stirred for 17 h at r.t.. A solution of 1N HCl (1 L) was then added and the organic phase was separated, washed with a saturated solution of Na<sub>2</sub>CO<sub>3</sub> (0.4 L) and dried over MgSO<sub>4</sub>. After concentration, the residue was purified by silica gel chromatography, eluting with 30% EtOAc/hexane to give the title compound as a white solid (133 g).

Step 6      5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl))-2-(5*H*)-furanone

A solution of the product from Step 5 (120 g) in CH<sub>2</sub>Cl<sub>2</sub> (1 L) was treated with DBU (81.6 g) and stirred for 1 h at r.t.. The reaction mixture was then treated with 1N HCl (550 mL) and the organic phase was separated, washed with saturated NaHCO<sub>3</sub> and dried over MgSO<sub>4</sub>. After concentration, the crude was swished with 20% EtOAc/hexane (450 mL), and filtered to give the title compound as a white solid (108.4 g, m.p. 172.7°C).

Analysis	Calculated	C 63.32; H 4.75
Found:		C 63.50; H 4.79

## ABBREVIATIONS

DBU	= 1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	= 4-(dimethylamino)pyridine
OXONE™	= 2KHSO <sub>5</sub> .KHSO <sub>4</sub> .K <sub>2</sub> SO <sub>4</sub>
THF	= tetrahydrofuran
TLMSCl	= trimethylsilyl chloride

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**WHAT IS CLAIMED IS:**

1. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition being suitable for  
5 once a day oral administration, said composition comprising 2.5 to 250 mg of a compound is 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone.

2. A composition according to Claim 1 comprising 5,  
10 10 or 25 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(5H)-furanone.

3. A composition according to Claim 1 comprising 10  
15 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(5H)-furanone.

4. A composition according to Claim 1 comprising 10  
20 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(5H)-furanone.

5. A composition according to Claim 1 comprising 10,  
25, or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(5H)-furanone.

25 6. A composition according to Claim 1 comprising 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-phenyl)-2-(5H)-furanone.

7. A pharmaceutical composition according to Claim 1,  
30 2, 3, 4, 5, or 6 further comprising  
(a) Microcrystalline cellulose,  
(b) Lactose monohydrate,  
(c) Hydroxypropyl cellulose,  
(d) Croscarmellose sodium, and  
35 (e) Magnesium stearate; or further comprising

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- 5 (a) Microcrystalline cellulose,  
(b) Lactose anhydrate,  
(c) Croscarmellose sodium, and  
(d) Magnesium stearate; or further comprising

Polyethylene oxide 400; or further comprising

- 10 (a) Sorbitol solution,  
(b) Polyvinylpyrrolidone,  
(c) Poly oxyethylene sorbitan monolaurate, and  
(d) Benzoic acid.

15 8. A method of treating an inflammatory disease  
susceptible to treatment with an non-steroidal anti-inflammatory agent  
comprising:  
administration orally once a day to a patient in need of such treatment  
2.5 to 250 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-  
methylsulfonyl)phenyl)-2-(5H)-furanone.

20 9. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment 5,  
10 or 25 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-  
methylsulfonyl)phenyl)-2-(5H)-furanone.

25 10. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment  
10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-  
methylsulfonyl)phenyl)-2-(5H)-furanone.

30 11. A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment  
10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)-  
phenyl)-2-(5H)-furanone.

35 12. A method according to Claim 8 comprising:

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administration orally once a day to a patient in need of such treatment 10, 25 or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone.

5                   13.    A method according to Claim 8 comprising:  
administration orally once a day to a patient in need of such treatment  
25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-  
methylsulfonyl)phenyl)-2-(5*H*)-furanone.

10                   14.    A method of treating an inflammatory disease  
susceptible to treatment with a non-steroidal anti-inflammatory agent  
comprising:  
administration orally once a day to a patient in need of such treatment a  
composition according to Claim 7.

15                   15.    A method according to Claim 9 for the treatment of  
non-chronic headache, pain or swelling.

20                   16.    A method according to Claim 12 for the treatment of  
osteoarthritis.

17.    A method according to Claim 13 for the treatment of  
rheumatoid arthritis..

25                   18.    Use of 2.5 to 250 mg of 5,5-dimethyl-3-(3-  
fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone  
in the manufacture of a once a day oral dosage form of a medicament  
for the treatment of an inflammatory disease susceptible to treatment  
with a non-steroidal anti-inflammatory agent.

30                   20.    Use according to Claim 18 of 5, 10 or 25mg of 5,5-  
dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-  
furanone in the manufacture of a once a day oral dosage form of a

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medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

21. Use according to Claim 18 of 10 to 125 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

22. Use according to Claim 18 of 10 to 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

23. Use according to Claim 18 of 10, 25 or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

24. Use according to Claim 18 of 10, 25 or 50 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of osteoarthritis.

25. Use according to Claim 18 of 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

26. Use according to Claim 18 of 25, 50 or 75 mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5H)-

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furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of rheumatoid arthritis.

27. Use according to Claim 18 of 5, 10 or 25mg of 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone in the manufacture of a once a day oral dosage form of a medicament for the treatment of non-chronic headache, pain or swelling.

28. A unit dose oral form which comprises from 5 to 22.5 mg of dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone.

29. A unit dosage form according to Claim 28 which comprises 12.5 or 20 mg of dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(5*H*)-furanone.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/07985

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/34

US CL :514/473

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/473

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

search terms: cyclooxygenase, furanone, inflammation, antiinflammatory, headache, pain, osteoarthritis, arthritis

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,474,995 A (DUCHARME ET AL) 12 December 1995, column 1, lines 54-56; column 6, line 16; column 63, example 12.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

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16 JULY 1997

Date of mailing of the international search report

12 AUG 1997

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